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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/018,870 | 04/18/2002 | Hee-Yong Lee | 5333-02600 | 8319 |

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| EXAMINER | |
|---|---|
| CHANNAVAJJALA, LAKSHMI SARADA | |
| ART UNIT | PAPER NUMBER |
| 1615 | |

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/018,870 | LEE ET AL. | |
| | Examiner | Art Unit | |
| | Lakshmi S Channavajjala | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,5,9-11,13,14 and 19-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,5,9-11,13,14 and 19-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Receipt of amendment and remarks dated 3-8-2004 is acknowledged.

Claims 1, 5, 9-11, 13, 14 and 19-36 are pending.

### *Claim Rejections - 35 USC § 112*

Claims 1, 5, 9-11, 13, 14 and 19-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Instant claim1 and claim 21 are amended to recite the limitations of biopharmaceutical compound over 5000 daltons, in an amount more than 10% by weight, which is not explicitly supported by the specification. Instant specification only states that the compound is over 2000 daltons and that the amount of compound is in the range of 0.1% and 90% respectively (page 6, line 7 and page 9, lines 15-20), but fails to exclude the molecular weight below 5000 and the amount of the compound below 10%. Thus, the exclusion of molecular weigh below 5000 daltons and a weight more than 10% constitute new matter. Examiner notes that applicants failed to show any support for the above amendments. Further, 11 and 33 recite the limitation "zero polysaccharide" that has not been described by the instant specification. Instant specification only describes the claimed compounds as polysaccharides and not as zero polysaccharides. Therefore, the above limitation constitutes new matter.

Claims 11 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Instant claims recite "zero polysaccharide", which is indefinite. It is unclear to the examiner as to what "zero polysaccharides" are. Instant specification does not provide any definition as to what are the meets and bounds of the term.

Claims 26 is rejected because instant claim recites that the compound is in the amount of 0.1% to 90%, whereas claim 21, from which the instant claim is dependent recites that the compound is above 10%.

Claim 24 recites the limitation "anionic" in line 3. There is insufficient antecedent basis for this limitation in the claim. Claims 28-30 are dependent from claim 24 and accordingly rejected as having insufficient antecedent basis.

Examiner notes that claim 5 and 27 recite polyoithoester, which is a typographical error. It appears that the

***Claim Rejections - 35 USC § 103***

Claims 1, 5, 9, 13-15, 19-29, 31, 32 and 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,470,582 to Supersaxo et al (Supersaxo) in view of US 4,046,750 to Rembaum OR Supersaxo in view US 6,326,021 to Schwendeman (Schwendeman).

Supersaxo et al. discloses a controlled release pharmaceutical composition comprising a physiologically active agent dispersed in preformed porous polymeric microparticles. The active agent concentration may be up to about 10% by weight to achieve controlled release. Each of the porous microparticles has a plurality of preformed pores into which active agent is loaded and from which the active agent is subsequently released to the environment of use. The compositions are capable of delivering physiologically effective amounts of active agent for at least 30 days. See abstract. The microparticles are polymer of polylactic, polyglycolic, or copolylactic/glycolic) acid and the active agent is a polypeptide. In a process for preparing the Pharmaceutical compositions, the preformed porous microparticles are suspended in a solution of the active agent. After the active agent has deposited on the microparticles, they are dried, and further processed as required to remain a stable, biologically active pharmaceutical composition. See col. 2, lines 4-34. After adding the active agent, the microparticles may be dried by freeze-drying. See col. 5, lines 40-43. The release rate may be controlled by co-incorporation of release rate modifying excipients and additives. Additionally, Supersaxo teaches that in the event the active agent is one that is deactivated by freeze-drying, a cryoprotectant may be added. Suitable excipients, additives, and cryoprotectants include proteins, such as serum albumin; carbohydrates, including simple sugars such as mannitol and sucrose and polysaccharides such as dextran, lipids and surfactants such as polysorbate 80, see page 4, lines 40-54. The microparticles, which may assume a variety of shapes, generally have diameters of from about 50 to about 400 microns and are extensively permeated with a network of pores into which the active agent is introduced. The active agent containing microparticle can be easily administered in various dosage forms. For example, an injectable formulation of the microparticles may be

dispersed in a suitable aqueous medium, optionally containing preservatives (e.g. methylparaben) and/or isotonizing agents (e.g. sodium chloride, sorbitol). The dose of the controlled release composition and the selection of suitable adjuvants, carriers, and solvents will depend upon the nature and amount of physiologically active agent in the microparticles, the dosage form, the desired duration of release, the recipient animal and purpose of the administration. Supersaxo does not disclose the microparticles having accessible ionic functional groups.

Supersaxo fails to teach biodegradable polymer with cationic functional groups.

Rembaum teaches binding of polyquaternary cationic polymeric segments to biocompatible porous particles containing halide or ternary amine sites forming modified beads. The beads offer a large positively charged surface area capable of binding polyanions such as heparin, DNA or bile salts or monoanions such as penicillin, pesticides etc., for slow release from the suspension and thus have a utility in clinical, diagnostic or analytical applications (col. 2). Rembaum teaches that the presence of hydroxyl, carboxy or amine groups on the microsphere beads permit covalent bonding of biomolecules such as haptens, enzymes, antibodies or lectins to the beads and the biomolecules bound can be used for diagnosis or treatment of a diseased condition. Examples 7-13 of Rembaum teach the preparation of microspheres containing aminofunctional groups.

Schwendeman teaches a method of making biocompatible base polymer particles that have functional groups attached on their surfaces. The process of preparing biocompatible polymer particles involves attaching a surface-active polymer on the base polymer such that the hydrophilic functional groups of the former demobilize the base polymer. The base polymers of

Schwendeman may be selected from biocompatible, biodegradable or bioresorbable polymers (col. 2,m lines 56-col. 3, lines 14), and the surface active polymer (SAFP) comprises a polymeric backbone with functional groups such as amines, hydroxyl, carboxylic, thiol etc., that are covalently bonded. Examples of SAFP include polylysine, polyglutamic acid etc (col. 3, lines 15-45). Schwendeman teaches preparing microspheres by solvent evaporation method and the resulting particles are in the same size range as claimed (col. 4, lines 1-30 and col. 4, lines 43-col. 5, lines 9). Schwendeman further teaches incorporating a drug by adding into the polymer particle, where the bioactive molecules may be attached to the SAFP (col. 4, lines 37-43).

It would have been obvious for one of an ordinary skill in the art at the time of the instant invention to add polymers or polymeric segments carrying cationic groups such as quaternary groups (Rembaum) or amines (Schwendeman) to the biocompatible or biodegradable polymers of Supersaxo so as to functionalized or add functional groups to the polymers, during the preparation of polymeric microspheres because Rembaum teaches that cationic modified microspheres are stable, do not coalesce in suspension, readily bind anionic molecules such DNA, RNA, heparin etc., penetrate quickly into living cells and allows covalent binding of biomolecules such as vitamins, enzymes to the polymers and hence are useful in diagnostic as well as therapeutic applications. Further, Schwendeman also suggests that attaching functional groups on the polymer during the microsphere formation enables targeting of the biomolecules to a particular tissue without altering the bulk properties of the polymer itself and yet achieve a slow release of the drug or biomolecules. Accordingly, a skilled artisan would have been motivated to modify the surface of the polymers of Supersaxo by adding cationic groups such as amines or quaternary amines with an expectation to improve the incorporation of biomolecules

into the microspheres and thus their tissue targeting as well as a slow and sustained release. Further, optimizing the amount of the drug to be incorporated, pH by adding an acidifying or an alkalizing agent, without affecting the ability to functionalized or attach the desired functional groups (cationic or anionic) to the polymer by routine experimentation would have been within the scope of a skilled artisan.

Claims 1, 10, 11, 21, 29-30, 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,470,582 to Supersaxo et al (Supersaxo) in view of Mady et al.

Supersaxo fails to teach the claimed surfactants. Mady studied effect of addition of surfactants to microsphere and observed that surfactants influence the nature of microsphere, structure, mecahnism of drug entrappment and release Mady teaches preparing Eudragit microspheres emoloying solvent evaporating technique. The microspheres of Mady contain an acidic drug ibuprofen and the surfactants cetrimide (cationic) or dioctyl sodium sulfosuccinate (DOSS, anionic) as anti-aggregating agents, in acidic aqueous phase. Mady teaches that the amount of initial drug released increased with an increase in the concentration of cetrimide and that the release pattern of the drug was smooth with 0.5% DOSS. Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to chose cationic surfactants such as cetrimide or anionic surfactants such as DOSS in the preparation of microspheres of Supersaxo because Mady suggests that the drug entrappment and release pattern are increased with the above surfactants. Thu, askilled artisan would have expected an increase in the drug loading and a smooth relelase of the drugs incorporated in the microspheres.

***Response to Arguments***

Applicant's arguments with respect to pending claims have been considered but are moot in view of the new ground(s) of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lakshmi S Channavajjala
Examiner
Art Unit 1615
October 1, 2004

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SUPERVISORY PATENT EXAMINER
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